ACUTE TOXICITY SUMMARY

NICKEL AND NICKEL COMPOUNDS

Molecular Formula	Molecular Weight	Synonyms	CAS Registry Number
Ni	59	elemental nickel	7440-02-0
NiO	74.69	nickel oxide	1313-99-1
$NiCl_2$	129.6	nickel chloride nickel dichloride	7718-54-9
$NiSO_4$	154.75	nickel sulfate nickelous sulfate	7786-81-4
$NiCO_3$	118.7	nickel carbonate carbonic acid nickel salt	3333-67-3
Ni_3S_2	240.19	nickel subsulfide trinickel disulfide heazlewoodite	12035-72-2

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **6 μg Ni/m³**
Critical effect(s) small decrements in airway function tests, especially in asthmatics
Hazard Index target(s) Respiratory System; Immune System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description Ni metal: silvery metal
NiO: black crystals
$NiCl_2$: yellow deliquescent crystals (U.S.EPA, 1985)
Density 8.9 g/cm^3 (Ni)
Boiling point 2730°C (Ni)
Melting point 1455°C (Ni); 1030°C ($NiCl_2$)
Vapor pressure not applicable for dust
Flashpoint not applicable
Explosive limits Nickel dust or powder is flammable (CDTSC, 1985).
Solubility Elemental nickel, nickel subsulfide, and nickel oxide are insoluble in water, but are soluble in dilute nitric, hydrochloric, and sulfuric acids. The chloride and sulfate forms of nickel are water soluble.
Odor threshold odorless
Metabolites Ni^{2+}

Conversion factor not applicable for fumes and dusts

III. Major Uses or Sources of Exposure

The most common airborne exposures to nickel compounds are to insoluble nickel compounds such as elemental nickel, nickel sulfide, and the nickel oxides from dusts and fumes. Contributions to nickel in the ambient air are made by combustion of fossil fuels, nickel plating, and other metallurgical processes. The most common oxidation state of nickel is the divalent (Ni^{2+}) form (U.S.EPA, 1985). Elemental nickel is a malleable, silvery-white metal that is highly resistant to strong alkali. Because of its corrosion resistance, nickel is used in the production of stainless steel, permanent magnets, and other alloys that require resistance to extremes of temperature or stress (U.S.EPA, 1985). Nickel is also used in electroplating baths, batteries, textile dyes, and catalysts (U.S.EPA, 1985). Nickel dust or powder is flammable (CDTSC, 1985). Nickel carbonyl also is airborne. However, because of its unique toxicity relative to the inorganic nickel compounds, this REL is not applicable to nickel carbonyl.

IV. Acute Toxicity to Humans

Soluble nickel compounds appear to be the greatest concern for acute health effects. The soluble forms of nickel are absorbed as Ni^{2+} (Coogan *et al*., 1989). Divalent nickel competes with copper for binding to serum albumin and is systemically transported in this way (Sunderman, 1986). The kidneys, lungs, and placenta are the principal organs for systemic accumulation of nickel (Sunderman, 1986). In contrast to the long half-life of the insoluble forms of nickel in the nasal mucosa, the elimination half-life of Ni^{2+} in the plasma is 1-2 days in mice (Nieboer *et al*., 1988).

Nickel fumes from high nickel alloy welding (mean concentration = 440 μg Ni/m³, range = 70-1,100 μg Ni/m³) caused complaints of upper respiratory irritation and headache in welders exposed for 4 weeks (Akesson and Skerfving, 1985).

A group of 7 metal plating workers with occupational asthma was evaluated for atopy and pulmonary function challenge in response to inhalational challenge with nickel and other metals (Cirla *et al*., 1985). Three of the asthmatics tested positive for the presence of nickel-specific IgE antibodies. Positive reactions to skin testing with nickel were found in 3 of the asthmatic workers who also had dermatitis. Six out of the 7 asthmatics exhibited significantly decreased FEV_1 (> 15%) when exposed to 0.3 mg/m³ nickel sulfate for 30 minutes. Control challenges with other metal salts did not reveal similar deficits in FEV_1.

Exposure to nickel in occupational settings causes dermatitis and asthma in some individuals with repeated exposures (Davies, 1986). The nickel ion, bound to proteins in the dermis, acts as an antigen eliciting a type IV (delayed type) hypersensitivity response. This response, mediated by T-lymphocytes, causes dermal sensitivity. This hypersensitivity can be diagnosed by patch testing (Menne and Maibach, 1989).

Predisposing Conditions for Nickel Toxicity

Medical: Asthmatics or atopic individuals may be especially at risk for developing nickel-induced asthma (Cirla *et al*., 1984). Cigarette smokers may receive greater nickel exposure, since cigarette smoke contains nickel (Reprotext, 1999). Additionally, a review of the literature on nickel toxicity showed that Ni^{2+} causes vasoconstriction in animals and humans which may potentiate the effects of a primary ischemic lesion in the cardiovascular system (U.S.EPA, 1985).

Chemical: In rats, rabbits, and dogs, 1 mg/kg nickel chloride antagonizes the cardiac arrhythmia induced by digoxin by competing with calcium at cardiac membrane sites (Prasad *et al*., 1980). The implications of this effect for persons with congestive heart failure have not been investigated.

V. Acute Toxicity to Laboratory Animals

Subacute (12-day) inhalation exposures (5 days/week, 6 hours/day) of 10 mice to nickel, as 10 mg Ni_3S_2/m^3, caused 100% mortality (Benson *et al*., 1987). Two of 10 rats also died from this exposure. Although no effect was seen on natural killer cell activity in these animals, lesions in the nasal and lung epithelium and in bronchial lymph node were observed. Pathology revealed emphysematous changes in the lungs of rats exposed to 5 or 10 mg Ni_3S_2/m^3, and fibrosis in mice exposed to 5 mg Ni_3S_2/m^3. Atrophy of lymphoid tissues, including spleen, thymus, and bronchial lymph nodes, was observed in mice and rats exposed to 5 or 10 mg Ni_3S_2/m^3.

Studies by Graham *et al*. (1975, 1978) indicate that the immune system is the most sensitive target for acute nickel toxicity. Mice (female, n = 14-29 per group) exposed by inhalation to 250 µg Ni/m^3 as $NiCl_2$ for 2 hours showed a significant decrease in splenic antibody-forming cells following a challenge with a T-lymphocyte dependent antigen (Graham *et al*., 1978). A similar suppression in antibody-forming cells was seen in mice exposed intramuscularly to 9.26 µg Ni/g body weight as $NiCl_2$ (Graham *et al*., 1975). Haley *et al*. (1987) showed that male cynomolgus monkeys, exposed to intratracheal Ni_3S_2 at a delivered dose of 0.06 µmol Ni/g lung tissue, had impaired pulmonary macrophage phagocytic function and increased natural killer cell activity. Mice also exhibited impairment of pulmonary macrophage function in addition to decreases in antibody-forming spleen cells with inhalation exposure to Ni_3S_2 or NiO (Haley *et al*., 1990). Natural killer cell activity measured by splenic cytotoxic activity to tumor cells as well as by clearance of melanoma tumors in vivo was suppressed in two strains of mice exposed to intramuscular injections of 18.3 mg Ni/kg as $NiCl_2$ as compared to controls (Smialowicz *et al*., 1985). The mechanism of nickel-induced immunotoxicity was not demonstrated in the above reports.

A host-resistance study by Adkins *et al*. (1979) showed that mice (80-120 per group) exposed to inhaled soluble nickel for 2 hours in the form of $NiCl_2$ or $NiSO_4$ were significantly more susceptible to mortality from streptococcal bacterial infection. The concentrations of nickel that showed these effects were 499 µg Ni/m^3 ($NiCl_2$) and 455 µg Ni/m^3 ($NiSO_4$). No significant change in mortality was seen with exposure to 369 µg Ni/m^3 as $NiCl_2$.

Nickel distributes preferentially to the lungs and kidneys following intratracheal administration of $NiCl_2$ to rats (Carvalho and Ziemer, 1982). The electrophilic Ni^{2+} ion is reported to be the causative agent of nephrotoxicity in rats; it binds to intracellular nucleophiles in kidney tissue such as guanine, adenine, and glutathione 2 hours following intraperitoneal exposure to 10 mg Ni/kg as $NiCO_3$ (Ciccarelli and Wetterhahn, 1984).

Subcutaneous injections of 10 mg/kg nickel chloride have been shown to increase prolactin secretion in rats 1 day following administration (Clemons and Garcia, 1981). However, an earlier study showed that prolactin secretion in rats is specifically inhibited for 30 minutes following intravenous exposure to 100 μg Ni^{2+} as $NiCl_2$ (LaBella *et al*., 1973).

VI. Reproductive or Developmental Toxicity

There is insufficient evidence for developmental or reproductive toxicity of nickel in humans. However, there are numerous reports of teratogenicity and other reproductive effects in laboratory animals exposed to nickel. Mice exposed during pregnancy to $NiCl_2$ by intraperitoneal injection bore offspring with numerous fetal malformations and skeletal anomalies (Lu *et al*., 1979). In addition there were increased fetal resorption rates and decreased fetal weights (Lu *et al*., 1979). Woollam (1972) showed that nickel acetate, when injected intraperitoneally into pregnant hamsters, caused significant fetal mortality at 25 mg/kg.

Intravenous exposure of pregnant rats to 11 mg Ni/kg caused increased fetal mortality and a 16% incidence of fetal malformations including anopthalmia, cystic lungs, and hydronephrosis (Sunderman *et al*., 1983). Temporary hyperglycemia was seen in pregnant rats exposed intraperitoneally to $NiCl_2$ at 4 mg/kg (Mas *et al*., 1985). The authors proposed that this hyperglycemia was a mechanism for teratogenicity.

Male rat reproductive toxicity (damage to epididymal tubules and abnormal spermatozoa) was observed followed a single subcutaneous dose of 5 mg/m³ mmol Ni/kg as Ni_3S_2 (Hoey, 1966). Benson *et al*. (1987) showed that mice and rats exposed to 5 or 10 mg Ni_3S_2/m³ displayed degeneration of testicular germinal epithelium after 12 days exposure (6 hours/day, 5 days/week).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure

Reference Exposure Level (protective against mild adverse effects): 6 μg Ni/m³

Study	Cirla *et al*., 1985
Study population	7 volunteer metal plating workers with occupational asthma
Exposure method	inhalation of 0.3 mg/m³ $NiSO_4 \cdot 6H_2O$ (67 μg Ni/m³)
Critical effects	significant (> 15%) decrease in FEV_1
LOAEL	67 μg Ni/m³
NOAEL	not observed
Exposure duration	30 minutes

Extrapolated 1 hour concentration	33 μg Ni/m³ ((67 μg Ni/m³)^1 * 0.5 h = C^1 * 1 h) (see Table 12 for information on "n")
LOAEL uncertainty factor	6
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	6
Reference Exposure Level	6 μg Ni/m³

For comparison with the immunotoxicity of nickel, an extrapolation from the 2-hour NOAEL in mice of 110 μg/m³ (Graham *et al*., 1978) to that of a 1-hour exposure was made using the time adjustment formula $C^n * T = K$, where n = 2. This yielded a 1 hour value of 160 μg/m³. Application of an uncertainty factor of 100 to account for interspecies and individual variation would result in a 1-hour REL of 1.6 μg Ni/m³. The Cirla *et al*. (1985) study was selected as the basis for the REL since the study group included sensitive humans (asthmatics), thus reducing uncertainty for this effect. This value should be reevaluated if human immunotoxicity data become available. The REL specifically does not apply to nickel carbonyl, which releases both nickel and carbon monoxide.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists a (revised) IDLH of 10 mg Ni/m³. It is based on acute inhalation toxicity data in mice, reported in a progress report on the toxicity of chemical warfare agents during World War II. An LC_{Lo} of 530 mg Ni/m³ was determined for a 10 minute exposure. This was time-adjusted to an equivalent 30 minute exposure of 92 mg Ni/m³ and divided by 10 to obtain a value of 9.2 mg Ni/m³, which was then rounded to 10 mg Ni/m³.

VIII. References

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